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Determinants of Exercise Capacity in Hypertrophic Cardiomyopathy

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Exercise capacity in hypertrophic cardiomyopathy is thought to relate to elevated left atrial pressure as a consequence of impaired diastolic function, but this assumption has not previously been evaluated. Twenty-three patients with hypertrophic cardiomyopathy underwent hemodynamic assessment during symptom-limited maximal exercise with objective measurement of exercise capacity by respiratory gas analysis. Maximal oxygen consumption and anaerobic threshold were 28.1 ± 7.5 and 21.5 ± 6.1 ml/kg per min, respectively (the lower limit of reference range in our laboratory is 39 and 27 ml/kg per min, respectively). Maximal oxygen consumption was reduced in 11 of 13 patients who were in New York Heart Association functional class I and who denied limitation of exercise capacity and in all 10 patients who were in functional class II or III. Maximal oxygen consumption and anaerobic threshold were related to peak cardiac index ($r = 0.650$, $p < 0.001$ and $r = 0.459$, $p = 0.03$, respectively) and to the increase in cardiac index on exercise ($r = 0.677$, $p < 0.001$ and $r = 0.509$, $p = 0.016$, respectively), but not to cardiac index at rest, peak and rest pulmonary capillary wedge pressure, pulmonary capillary wedge pressure at an oxygen consumption of 15 ml/kg per min or the rise in pulmonary capillary wedge pressure on exercise. These findings are not consistent with the hypothesis that elevated left atrial pressure is the major determinant of exercise capacity in patients with hypertrophic cardiomyopathy and they suggest that, as in patients with chronic cardiac failure, other mechanisms should be considered.

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In hypertrophic cardiomyopathy, dyspnea is common (1–3), diastolic function often impaired (4,5) and left atrial pressure elevated (6). Dyspnea has been considered to be a consequence of a rapid increase in left atrial pressure as a result of impaired diastolic filling at high heart rates (7–9). To test the assumption that exercise capacity is limited by left-sided filling pressures, we measured pulmonary capillary wedge pressure and cardiac output on exercise and related them to objective assessment of exercise capacity in patients with hypertrophic cardiomyopathy.

Methods

Study patients. Twenty-six consecutive patients with hypertrophic cardiomyopathy were considered for entry to the study. Three were excluded for the following reasons: pulmonary disease in one, severe mitral regurgitation in one and inability to exercise due to painful liver congestion in another. The remaining 23 patients in whom exercise was limited only by dyspnea or fatigue were studied. Thirteen were in New York Heart Association functional class I, 8 in class II and 2 in class III. They were aged 15 to 70 (median 30) years. Twenty-two patients had sinus rhythm and one had well controlled atrial fibrillation. All underwent conventional two-dimensional echocardiographic (10,11), Doppler (12), radionuclide (13) and ambulatory electrocardiographic (14) assessment (Table 1). The clinical diagnosis of hypertrophic cardiomyopathy was confirmed by the echocardiographic demonstration of unexplained left ventricular hypertrophy (15). Patients with sustained hypertension (>150/90 mm Hg) were excluded. Twenty-three age- and gender-matched normal volunteers also entered the study and underwent exercise testing with respiratory gas analysis, but not hemodynamic assessment.

Exercise testing. Before the study all subjects underwent at least three practice exercise tests. When maximal oxygen consumption in two consecutive exercise tests differed by

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Table 1. Clinical, Echocardiographic, Radionuclide and Electrocardiographic Criteria in 23 Patients With Hypertrophic Cardiomyopathy

Patient No.	Age (yr) & Gender	NYHA Class	Rx	Max WT (mm)	LA (mm)	LVEDD (mm)	Pattern	RVH	PG (mm Hg)	EF (%)	PER ($EDV \cdot s^{-1}$)	PFR ($EDV \cdot s^{-1}$)	SVT	VT
1	45M	I	CCB	23	35	36	ASH	No	64	80	4.49	3.42	No	Yes
2	25F	III	None	26	49	37	ASH	Yes	42	79	3.50	3.03	Yes	No
3	41M	II	None	22	30	48	ASH	Yes	42	81	3.93	2.81	Yes	Yes
4	23F	I	None	15	28	36	ASH	No	—	67	3.93	4.91	No	No
5	70F	II	CCB	15	40	40	Symm	No	30	85	5.13	6.55	Yes	No
6	25F	II	None	21	40	40	ASH	No	<20	65	4.56	4.29	No	Yes
7	35M	I	CCB,BB	27	39	45	ASH	No	<20	81	3.70	2.55	No	No
8	30M	I	None	20	31	47	ASH	No	<20	79	3.84	2.65	No	No
9	42M	II	None	23	60	41	ASH	No	64	—	—	—	No	No
10	30F	I	None	22	42	36	ASH	No	<20	92	4.79	5.13	Yes	No
11	26M	I	A	19	40	42	Distal	No	<20	65	4.93	2.07	No	No
12	42M	I	None	20	43	45	ASH	No	100	71	3.32	2.38	Yes	No
13	51M	I	None	23	53	50	ASH	Yes	<20	65	4.61	2.33	No	No
14	23F	II	None	21	33	41	Distal	No	<20	85	5.64	4.62	No	No
15	15F	II	None	30	40	48	ASH	No	<20	74	4.45	3.35	No	No
16	25M	II	None	29	44	43	ASH	Yes	<20	68	3.50	4.70	Yes	Yes
17	22M	I	None	20	32	41	ASH	No	<20	78	3.83	2.46	No	No
18*	44M	III	A	24	57	55	ASH	No	<20	44	2.45	1.89	Yes	Yes
19	21M	I	None	23	38	39	ASH	No	—	84	3.60	2.76	No	No
20	41M	II	None	21	35	54	ASH	Yes	<20	—	—	—	No	No
21	49F	I	A,BB	20	35	39	ASH	No	77	77	2.85	2.21	No	No
22	54F	I	None	19	31	50	Distal	Yes	<20	—	—	—	No	No
23	29M	I	None	27	45	41	ASH	No	55	—	—	—	No	No

*Patient with atrial fibrillation. A = amiodarone; ASH = asymmetric septal hypertrophy; BB = beta-blocker; CCB = calcium channel blocker; EDV = end-diastolic volume; EF = ejection fraction; F = female; LA = left atrium; LVEDD = left ventricular end-diastolic dimension; M = male; Max WT = maximal wall thickness; NYHA = New York Heart Association classification; PER = peak ejection rate; PFR = peak filling rate; PG = calculated Doppler pressure gradient (12); RVH = right ventricular hypertrophy; Rx = treatment; SVT = supraventricular tachycardia; Symm = symmetric; VT = ventricular tachycardia.

<5%, the subject was considered to be practiced in the technique.

On the day of the study, patients arrived having fasted and taken their usual medications. A Swan-Ganz catheter was inserted into a subclavian vein under local anesthesia and advanced into the pulmonary artery. After 1 h of rest patients underwent symptom-limited treadmill exercise according to a modified Bruce protocol with simultaneous respiratory gas analysis performed with use of an Airspec 200MGA mass spectrometer linked to a BBC microcomputer with an analog to digital converter by an established technique (16). Sampling of mixed expired gases was performed every second and data were expressed as 10 s means. A printout of minute ventilation, oxygen consumption, carbon dioxide production and respiratory quotient was obtained. Maximal oxygen consumption was defined as the mean of the highest two values of oxygen consumption obtained during exercise. Anaerobic threshold was determined by one of the conventional methods (17). In brief, the mean value and 2 SD for all of the 10 s respiratory quotient values ≤50% of maximal oxygen consumption were calculated. At higher work loads carbon dioxide production increases disproportionately relative to oxygen consumption with a consequent rise in respiratory quotient. When two of three consecutive respiratory quotient measurements lay outside 2 SD from the mean value obtained at lower work loads, the oxygen consumption at the first of these measurements was defined as the anaerobic threshold.

Pulmonary artery systolic and pulmonary capillary wedge pressures and cardiac output were measured with the patient supine and erect before exercise and erect during each minute of exercise. Pressures were measured by Gould-Statham transducers referenced to atmosphere at mid-chest level, and recorded on a Mingograf 7 multichannel recorder. Cardiac output was determined by the Fick method as:

$$\text{Cardiac output (liters/min)} = \frac{\text{maximal oxygen consumption (ml/min)} \times 10}{\text{hemoglobin (g/dl)} \times 1.34 \times \text{arteriovenous oxygen difference}}.$$

Statistical methods. Data are expressed as mean values ± 1 SD unless otherwise stated. Statistical analysis was performed with Student's *t* test for paired data and with correlation coefficient and linear regression when appropriate.

Table 2. Exercise Capacity and Hemodynamics in 23 Patients With Hypertrophic Cardiomyopathy

Patient No.	VO_2 max (ml/kg per min)	AT (ml/kg per min)	PCWP (mm Hg) At Rest	PCWP (mm Hg) At VO_2 of 15 (ml/kg per min)	PCWP (mm Hg) Peak	CI (liters/min per m^2) At Rest	CI (liters/min per m^2) At Peak Ex
1	24.39	17.05	5	17	48	2.07	5.60
2	22.37	18.43	12	16	28	3.13	7.14
3	21.53	17.70	0	5	18	2.58	8.26
4	36.32	34.20	0	22	22	2.26	8.06
5	21.46	20.81	7	12	17	2.00	9.08
6	24.80	15.81	0	9	12	3.00	10.16
7	20.69	13.79	0	12	18	3.98	7.0
8	34.75	22.39	0	13	32	2.35	8.78
9	21.68	16.08	0	18	25	1.16	5.41
10	25.26	15.71	0	25	37	2.3	6.92
11	42.00	24.00	6	25	30	1.77	9.95
12	30.00	24.8	17	37	35	3.42	7.88
13	28.83	25.2	10	16	28	1.95	9.5
14	23.54	20.55	6	20	20	2.05	4.3
15	30.77	NA	2	NA	7	2.33	7.94
16	22.05	20.07	15	35	40	1.7	5.28
17	35.84	25.70	2	12	17	1.93	11.42
18	18.49	18.04	15	27	27	2.06	6.37
19	42.30	31.20	0	0	12	2.55	13.0
20	22.20	16.60	6	17	20	2.66	8.9
21	21.30	14.90	0	22	40	2.62	7.55
22	38.80	35.30	2	2	8	2.36	8.44
23	36.80	23.70	8	7	17	2.44	9.33
Mean SD	28.09 ± 7.53	21.46 ± 6.1	4.91 ± 5.58	16.77 ± 9.58	24.26 ± 10.88	2.38 ± 0.6	8.1 ± 2.04

AT = anaerobic threshold; CI = cardiac index; Ex = exercise; NA = not available; PCWP = mean pulmonary capillary wedge pressure; VO_2 max = maximal oxygen consumption.

Results

Maximal oxygen consumption and anaerobic threshold. Exercise was terminated by breathlessness rather than fatigue in all patients, and was completed without complication. Maximal oxygen consumption and anaerobic threshold for the patients were 28.1 ± 7.50 and 21.5 ± 6.1 ml/kg per min, respectively. Maximal oxygen consumption and anaerobic threshold in the age- and sex-matched normal subjects were 39 to 68 (mean 47) and 27 to 58 (mean 41) ml/kg per min, respectively (Table 2).

Correlation with pulmonary capillary wedge pressure and cardiac index. Mean pulmonary capillary wedge pressure of patients in the supine position and at rest was 15 ± 5 mm Hg. Erect mean pulmonary capillary wedge pressure increased from 5 ± 5 mm Hg at rest to 24 ± 11 at peak exercise ($p < 0.001$) and cardiac index increased from 2.4 ± 0.6 liters/min per m^2 at rest to 8.1 ± 2.1 at peak exercise ($p < 0.001$) (Table 2).

Maximal oxygen consumption and anaerobic threshold were related to the peak cardiac index and the increase in cardiac index on exercise but not to cardiac index at rest. They were not related to either rest or peak pulmonary capillary wedge pressure, the change in pulmonary capillary wedge pressure on exercise, or the pulmonary capillary wedge pressure at the time when oxygen consumption was 15 ml/kg per min (Table 3, Fig. 1 and 2).

Other correlations. Exercise capacity was not related to conventional radionuclide indexes of systolic or diastolic function or to echocardiographic left atrial size, left ventricular end-diastolic dimension or maximal wall thickness.

Table 3. Relation of Exercise Capacity to Hemodynamic Variables in 23 Patients

	VO_2max r	VO_2max p	AT r	AT p
CI				
At rest	−0.113	NS	−0.157	NS
Peak	0.650	<0.001	0.459	=0.03
Change on exercise	0.6771	<0.001	0.509	=0.016
PCWP				
At rest	−0.212	NS	0.008	NS
Peak	−0.297	NS	−0.378	NS
Change on exercise	−0.197	NS	−0.378	NS
At VO_2 of 15 ml/kg per min	−0.301	NS	−0.232	NS

Abbreviations as in Table 2.

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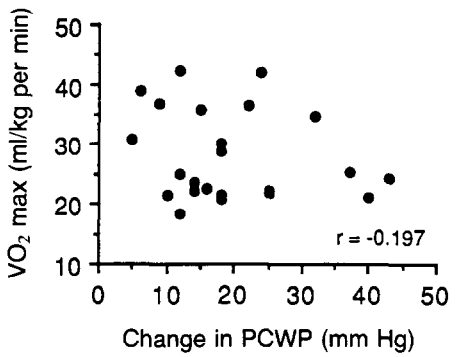

Figure 1. Relation of maximal oxygen consumption (VO_2 max [ml/kg per min]) and the change in pulmonary capillary wedge pressure (PCWP [mm Hg]) from rest to peak exercise.

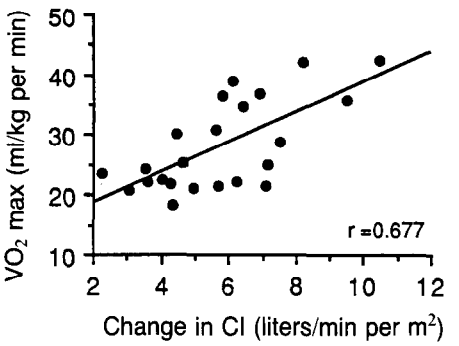

Figure 2. Relation of maximal oxygen consumption (VO_2 max [ml/kg per min]) and the change in cardiac index (CI [liters/min per m^2]) from rest to peak exercise.

Discussion

Dyspnea in hypertrophic cardiomyopathy. Breathlessness was the limiting symptom in all 23 patients studied. Exercise capacity as assessed by maximal oxygen consumption was moderately impaired in all but 2 patients, even though 13 were in functional class I and claimed normal exercise tolerance. This finding serves to emphasize the limitation of specific activity scales in the assessment of exercise capacity, particularly in patients with long-standing disability. It has been stated that the most common symptom in hypertrophic cardiomyopathy is shortness of breath resulting from an increased left atrial pressure caused by the stiff left ventricle and its high diastolic pressure (7–9). Observation of a patient (Table 2, Patient 3) with marked exercise dyspnea associated with normal rest and peak exercise pulmonary capillary wedge pressures led us to question this hypothesis.

Role of cardiac output and left atrial pressure during exercise. This study demonstrates that exercise capacity in hypertrophic cardiomyopathy is related to cardiac output, as it is in normal subjects and patients with heart failure (17,18). It also confirms previous reports (7–9) of an abnormal increase in left atrial pressure on exercise in hypertrophic cardiomyopathy. If the magnitude of the rise in left atrial pressure was a major determinant of exercise capacity, then one would expect a statistical relation to exist between the two. In this group of 23 patients with hypertrophic cardiomyopathy, exercise capacity was not related to pulmonary capillary wedge pressure measured at rest, at peak exercise or at a submaximal oxygen consumption value of 15 ml/kg per min, or to the increase in pulmonary capillary wedge pressure from rest to peak exercise. We therefore conclude that, in the patients studied, left atrial pressure was not a major determinant of exercise capacity.

Do these findings apply to other patients with hypertrophic cardiomyopathy? In this regard, the exercise capacity and pulmonary capillary wedge pressure at rest of the 23 patients are representative of larger consecutive series (6,19). In patients with severe mitral regurgitation, the increase in left atrial pressure would be expected to be of greater importance in determining exercise capacity. Although mild to moderate mitral regurgitation is common in hypertrophic cardiomyopathy (20,21), severe mitral regurgitation is rare (21,22) and one patient with this condition was excluded at the time of initial screening. Thus, our findings are probably applicable to patients with hypertrophic cardiomyopathy in general, with the exception of patients with significant mitral regurgitation. Although this finding is contrary to traditional teaching, it is perhaps not surprising because in chronic heart failure there is similarly no relation between exercise capacity and left atrial pressure (17,23), and other factors have been shown to be important.

Metabolic changes during exercise. Studies in patients with chronic heart failure have demonstrated that the symptom that terminates exercise (that is, breathlessness or fatigue) depends on the type of exercise performed, and it has been suggested (17) that metabolic changes during exercise may contribute to the hyperventilatory response. Ultrastructural and histochemical changes have been demonstrated in limb skeletal muscle in patients with chronic heart failure (24). It has been proposed (25) that these changes may be due to impaired oxygen delivery to skeletal muscle. Although therapeutic interventions in patients with chronic heart failure may result in rapid improvement in hemodynamic variables, there is a considerable delay before an objective increase in exercise capacity can be detected (26,27). This delay has led to the suggestion (28) that stiffness of small blood vessels, perhaps as a result of edema of the vessel wall, may contribute to inadequate oxygen delivery to skeletal muscle, which may take time to resolve, thus explaining the delayed improvement in exercise capacity. In patients with hypertrophic cardiomyopathy, treatment with verapamil has been shown to be associated with prolongation of treadmill exercise duration at 5 days (29), and edema of the blood vessel wall is therefore unlikely to be an

important factor. The relation of exercise capacity and cardiac index is, however, consistent with the concept that skeletal muscle blood flow may be a limiting factor.

Respiratory muscle fatigue. Respiratory muscle fatigue may contribute to the perception of breathlessness in normal subjects (30) and in patients with obstructive airways disease (31). It is possible that inadequate oxygen delivery to respiratory muscle may occur in patients with heart disease and result in premature respiratory muscle fatigue. Abnormal respiratory muscle function has been demonstrated in patients with mitral stenosis, but it is not clear whether this relates to the loss of respiratory muscle bulk as a consequence of cachexia (32). The possible role of premature respiratory muscle fatigue in patients with hypertrophic cardiomyopathy has not been investigated.

Subjective factors. Breathlessness is a subjective sensation, and perception of it may differ from patient to patient in much the same way as pain threshold varies. Thus, although each subject continues to exercise to a perceived maximal tolerance of dyspnea, the latter may vary from patient to patient. Administration of dihydrocodeine to patients with chronic obstructive airways disease has been shown to relieve the sensation of breathlessness and increase exercise tolerance (33). Thus, central modulation may play an important role in determining the sensation of breathlessness and, therefore, exercise capacity. This area has not been explored in patients with heart disease.

Conclusions. Contrary to the commonly accepted belief, the increase in left atrial pressure does not appear to be a major determinant of exercise capacity in hypertrophic cardiomyopathy. The role of other factors, including those described in this study, requires further investigation.

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